REMARKS

Claims 1, 2, 4-22 and 28-33 and 37-47 are pending in the present application. Specifically claims 23-27 have been cancelled, without prejudice or disclaimer, and new dependent claims 37-47 have been added. Support for claims 37-39, which are identical to previously presented but unentered claims 34-36, can be found, *inter alia*, on page 3 lines 2 and 21 and/or page 10, second table, where batches A-F have pH's ranging from 5.53 to 6.19. Support for claims 40-47 can be found, inter alia, on page 6 lines 2-5 and lines 30-33; and page 7 lines 11-16. Accordingly, no new matter has been introduced by the above-amendment.

**The Present Invention**

According to U.S. 4,572,909, Campbell *et al.* at Pfizer invented amlodipine and various salts thereof in the early 1980's. The most preferred salt of amlodipine at that time was amlodipine maleate (See column 2 lines 10-11 of US '909). Indeed, Pfizer intended to market amlodipine maleate and even conducted clinical studies with amlodipine maleate formulations according to the publicly available "Review of an Original NDA", NDA No. 19-787 (the FOIA material). However, according to the FOIA material, Pfizer switched from the original amlodipine maleate to amlodipine besylate because the maleate salt form had "formulation (tabletting) and stability problems." (See page 2 lines 1-8 of the FOIA material). U.S. 4,879,303 to Davison *et al.* of Pfizer shows that this switch was a patentable way to solve these problems with amlodipine maleate. Note that column 1 lines 25-26 points out that maleate was disclosed in US '909 as being particularly preferred while column 2 line 47 through column 3 line 10 teach

amlodipine maleate's inferior stability to amlodipine besylate. Thus, to solve the problem with amlodipine maleate, Pfizer replaced it with a different salt, namely amlodipine besylate.

The present invention is based in part on the discovery of how to solve the amlodipine maleate stability problem recognized in the prior art. Rather than switch salts as the originator did, the present applicants discovered that controlling the pH to a specified range can improve the stability of an amlodipine maleate composition. By controlling the pH, the formation of a previously unknown but problematic impurity, called amlodipine aspartate in this application, can be reduced, thereby improving the stability of the composition. Indeed, unlike the results shown in Davison (US '303) where the amlodipine maleate composition was much less stable than amlodipine besylate, the amlodipine maleate composition of the present invention can be as stable or more stable than amlodipine besylate. For instance, a comparison of stability studies for inventive compositions (A) and (B) (page 17 of the instant specification) with stability studies for commercially available amlodipine besylate (page 18 of the instant specification) shows that the amount of amlodipine present in the formulation drops less over three months in samples (A) and (B) than in the NORVASC® samples. The drop in amlodipine reflects degradation/reaction of the amlodipine during the accelerated storage conditions into other compounds such as amlodipine aspartate, etc.; thus, the lesser the change in amlodipine amount, the greater the stability of the composition. Accordingly, applicants have solved a recognized and notable problem in the art.

**Rejection over Davison**

Claims 1, 2, 4-9, 11, 14-18, and 22 have been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al., US 4879303, (US '303). This rejection is

respectfully traversed. Specifically, this rejection is based on several erroneous factual assertions and incorrect legal standards.

**Factual Errors**

First, the Examiner asserts that column 2 lines 22-31 of US '303 teaches that a solid pharmaceutical composition should have a pH close to that of blood. This is untrue. The pH refers to that of an aqueous solution – not a solid composition as is recited in claim 1. Specifically, column 2 teaches that "salts which provide solutions having a pH close to that of blood (7.4) are preferred because they [the salts] are readily biocompatible and can easily be buffered to the required pH range without altering their solubility" (emphasis added). Thus this passage deals only with pH in terms of an aqueous solution, one which has or can be buffered to have a pH close to that of blood. With this aqueous solution in mind, US '303 uses pH as guidance for picking the best salt. There is no teaching or suggestion in this passage of selecting a pH for a solid form pharmaceutical composition. The Examiner's statement of the teaching in US '303 is erroneous.

Secondly, the Examiner asserts that column 2 line 47 of US '303 teaches that selecting the pH will provide good stability (see for instance page 3 last four lines of the final office action dated May 5 2003). But US '303 makes no such connection between pH and stability. Line 47 merely states the general proposition that "[g]ood stability in the solid state is very important for tablets and capsules, whilst good stability in solution is required for an aqueous injection."[1] There is no mention of pH. There is no mention of blood or compatibility therewith. Nothing in column 2 lines 47-50 link solid state stability with pH as the Examiner surmises.

Thirdly, the Examiner asserts that calcium phosphate inherently provides a pH within the applicants' claimed range and that applicants have merely argued to the contrary without providing a factual basis. Apparently the Examiner has overlooked page 6 of the instant specification where the pH variation among different types and grades of calcium phosphate are discussed. The Examiner has supplied no basis to doubt the objective truth of these statements. Nonetheless, applicants provide herewith extracts from the Handbook of Pharmaceutical Excipients, 3rd Edition, regarding various calcium phosphates. As the Examiner will note, the pH for Calcium Phosphate Dibasic Anhydrous is listed under typical properties as 7.3 and 5.1. As applicants stated in the specification, the pH depends on which dibasic calcium phosphate anhydrate is used as to what the pH is. For the dihydrate, the pH is simply listed as 7.4. Thus, merely identifying dibasic calcium phosphate in a composition does not necessarily mean that the pH of the composition is less than 6.8 as the Examiner repeatedly asserts.

**Legal Errors**

Among the legal errors committed by the Examiner, two are prominent. First, the Examiner dismisses the unexpectedly superior showing regarding stability of the claimed amlodipine maleate compositions because the claims do not recite improved stability (see page 5 lines 15-17 of the final office action of May 5, 2003). But the law does not require applicants to recite advantages that flow from the claimed invention. Instead, the claims need only recite the structure/function that provides those advantages. *In re Merchant*, 575 F.2d 865, 869 (CCPA 1978)("We are aware of no law requiring that unexpected results relied upon for patentability be recited in the claims. . . Moreover, the 'feature' responsible for appellant's unexpected results is

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[1] Notice that aqueous solutions are characterized separately from solid compositions, which emphasizes the distinction between the two. This provides all the more evidence that the passage of column 2 lines 22-31 is dealing

recited in the claims, viz., 'substantially anhydrous.'"); *Ex parte Rinderer*, appeal No. 2000-1651, 2002 WL 465339 (BPAI 2002)("In order to distinguish the claims over the prior art, an applicant is not required to recite the advantages flowing from the claimed invention; rather the claims must include the structure which provides those advantages"). In the instant application, the claims recite the feature from which the unexpected results flow, namely controlling the pH to the specified range.

Secondly the Examiner misapplies the notion of a showing being not commensurate in scope with the claims. "The nonobviousness of a broader claimed range can be supported by evidence based on unexpected results from testing a narrower range if one of ordinary skill in the art would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof. *In re Kollman*, 595 F.2d 48, 201 USPQ 193 (CCPA 1979)." MPEP 716.02(d). For a range, criticality is normally established by comparing values inside and outside the claimed range (Vanderheijden declaration compares above and below claimed range with four values within claimed range). See MPEP 716.02(d) last paragraph. Finally, that the Examiner can propose variables which may affect the unexpected results is not a valid basis to disregard the showing. Instead, the Examiner must provide more than mere speculation. *Ex parte Nieh*, Appeal No. 1999-0381, 2002 WL 1801386 (BPAI 2002)("Assuming arguendo that these factors may have some effect, the examiner has provided no evidence to substantiate that they are of any significance. The examiner's position is speculative in nature absent an explanation or evidence of record of why these factors would be expected to affect the results to such a degree that the declaration evidence would be of minimal value").

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exclusively with aqueous solutions (and which salts form them best) when it discusses biocompatibility.

**No Prima Facie Case of Obviousness**

In view of the above errors, the Examiner has clearly failed to establish a *prima facie* case of obviousness. Because the pH disclosure in US '303 refers to an aqueous solution and is not tied to a solid composition as per the present claims, the Examiner has no motivation to select a pH of around blood or any other pH. Similarly, there is no motivation or expectation that stability for the amlodipine maleate salt compositions can be enhanced by controlling the pH, much less of controlling the pH to the claimed range. And the mere mention of calcium phosphate as an excipient does not inherently render the composition within the claimed pH range. This is proven by the extracts from the Handbook of Pharmaceutical Excipients. It is also noteworthy that the commercial amlodipine besylate which is believed to contain mostly microcrystalline cellulose and calcium phosphate as excipients exhibits a pH of greater than 7 (see page 6 lines 7-8 of the present specification). Thus, the creation of an amlodipine maleate formulation does not inherently (i.e. necessarily) form a composition having a pH within the claimed range. Given the absence of any motivation leading the worker skilled in the art to the applicants' claimed pH range in a solid composition and given that such a pH is not inherently produced in making an amlodipine maleate composition, even one that contains calcium phosphate, the creation of the presently claimed invention would not have been obvious.

**Secondary Considerations – The Invention as a Whole**

Aside from the lack of motivation, US '303 teaches away from making amlodipine maleate compositions. The point of the teachings is that maleate is too unstable in a solid composition (see table in column 3). This is why the US '303 patent finds that besylate is the best salt even though maleate had originally been the top candidate.

Similarly, since the FOIA material and the US '303 informed the world of the problems with amlodipine maleate, applicants are the first to bring forward a solution to the amlodipine maleate problems. Overcoming a long felt but unresolved need is further evidence of unobviousness.

Lastly the stability exhibited by the claimed amlodipine maleate compositions is unexpected good. According to US '303 an amlodipine maleate solid composition should exhibit inferior stability to an amlodipine besylate composition. But the data in the present specification shows that the stability of the claimed amlodipine maleate is equal to or better than the stability of the commercial product NORVASC®. The following table presents some of the data from pages 17 and 18 of the present specification for the Examiner's convenience.

| Month | (A)<br>mg of Amlodipine | NORVASC® 2.5mg<br>mg of Amlodipine |
|---|---|---|
| 0 | 2.45 | 2.44 |
| 3 | 2.40 | 2.34 |

Thus at storage in open dish at 40°C/75%RH, inventive sample A lost 0.05 mg of amlodipine during three months while the commercial amlodipine besylate lost 0.1 mg of amlodipine. This is not the expected result given the teachings of the prior art. The teachings in US '303 in particular raise the expectation that amlodipine maleate formulations should be inferior (i.e. lose more amlodipine) than amlodipine besylate formulations.

And applicants have established the criticality of the claimed range by comparing four compositions within the claimed range and two outside of the range (one above and one below).

The data from the Rule 132 declaration is summarized again below for the Examiner's convenience.

Table 2A

Difference in Impurities Between 40°C/75% RH and Baseline After 1 month, Open Dish

| | A<br>pH 7.2 | B<br>pH 6.36 | C<br>pH 6.07 | D<br>pH 5.95 | E<br>pH 5.8 | F<br>pH 5.19 |
|---|---|---|---|---|---|---|
| Δ Aspartate[1] | 5.11 | 1.55 | 0.30 | 0.07 | 0.06 | 0.05 |
| Δ Amide[2] | 0 | 0 | 0 | 0 | 0.04 | 0.13 |
| Δ Pyridine[3] | 0.09 | 0.05 | 0.03 | 0.05 | 0.10 | 0.13 |
| Δ Total Impurities | 5.68 | 1.73 | 0.4 | 0.19 | 0.25 | 0.42 |

1. amlodipine aspartate (Z#204)
2. amlodipine amide (Z#205)
3. amlo-pyridine (Z#202)

The data shows and confirms the overall trend reported in the instant specification, namely that the stability 'sweet spot' for a solid amlodipine maleate is a pH between 5.5 and 6.8. At a pH of 7.2 the amount of aspartate formed significantly increases (see tablet A). As explained on page 3 of the specification, it is believed that the aspartate is formed in the solid composition via a Michael addition, which needs an alkaline environment. On the other hand, as the pH drops below 5.5, the formation of other impurities, such as amlo-pyridine, increases. Thus, applicants are claiming the optimized pH range for reducing the risk of instability.

According to the Examiner's logic, tablet A at pH of 7.2 should have had the best stability because it is closest to blood pH. But instead it has the worst stability. Clearly the data shows a trend wherein the worker skilled in the art would understand that a composition at pH of 6.8 will have significantly better stability than the tablet A at pH of 7.2. The data is thus reasonably commensurate in scope with the claims. Because the data is the opposite of what the

Examiner believes US '303 teaches, it is necessarily unexpected. Unexpected superiority is strong evidence of non-obviousness. And the Examiner has failed to provide any basis for believing that compositions with different excipients but having the same overall pH would behave significantly differently and thus does not have a proper criticism of the data. *Ex parte Nieh, supra.* Indeed, applicants *have* supplied an explanation as to why pH is a good measure of the invention, based on the chemistry involved. The Examiner needs more than mere speculation to dismiss the applicants' showing of unexpected results.

In view of the failures of in US '303 to suggest the claimed amlodipine maleate composition or the advantages derived therefrom, the presently claimed subject matter is not obvious within the meaning of 35 U.S.C. § 103 and reconsideration and withdrawal of this rejection are respectfully requested.

**Rejection over Davison in view of EP 0089167**

Dependent claims 12 and 13 have been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303) in view of EP 0089167. This rejection is respectfully traversed.

This rejection is in error for at least the reasons set forth above regarding the failures of Davison. Inasmuch as Davison in deficient to render claim 1 unpatentable and EP 0089167 is not asserted to overcome these deficiencies, the instant rejection of dependent claims 12 and 13 is likewise improper. Reconsideration and withdrawal of this rejection are respectfully requested.

**Rejection over Davison in view of Sherwood**

Dependent claims 10, 19 and 20 have been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303) in view of Sherwood et al. (US 5585115). This rejection is respectfully traversed.

This rejection is in error for at least the reasons set forth above regarding the failures of Davison. Inasmuch as Davison in deficient to render claim 1 unpatentable and Sherwood is not asserted to overcome these deficiencies, the instant rejection of dependent claims 10, 19 and 20 is likewise improper. Reconsideration and withdrawal of this rejection are respectfully requested.

**Rejection over Davison in view of Sherwood and further in view of Schobel**

Dependent claim 21 has been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303) in view of Sherwood et al. (US 5585115) and further in view of Schobel (US 4687662). This rejection is respectfully traversed.

This rejection is in error for at least the reasons set forth above regarding the failures of Davison. Inasmuch as Davison in deficient to render claim 1 unpatentable and Sherwood and Schobel are not asserted to overcome these deficiencies, the instant rejection of dependent claim 21 is likewise improper. Reconsideration and withdrawal of this rejection are respectfully requested.

**Rejection over Davison in view of Schobel**

Claims 23-27 have been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303) in view of Schobel (US 4687662). This rejection is respectfully traversed.

While the Examiner has misunderstood the teaching of Schobel, wherein a granulate of excipients and a therapeutic agent is taught to have a particle size of 100 to 600 microns but no teaching regarding the particle size of the therapeutic agent itself is provided, these claims have been cancelled to expedite prosecution. Applicants are considering filing a divisional application directed to this subject matter. Thus, while applicants do not agree with the propriety of this rejection, the above amendment has nonetheless rendered the rejection moot. Reconsideration and withdrawal thereof are respectfully requested.

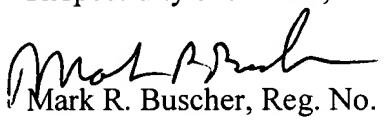
**Conclusion**

In view of the above-amendments and remarks, all claims are directed to novel, patentable subject matter. Reconsideration of the rejections and allowance of the application are respectfully requested.

Should the Examiner have any questions regarding this application, she is encouraged to contact Mark R. Buscher (Reg. No. 35,006) at telephone No. 703 753 5256.

Please charge any shortage in fees, or any overpayment, in connection with this filing, including extension of time fees, to Deposit Account No. 50-2877.

Respectfully submitted,



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